2007年3月24日 (土曜日)

第5回臨床腫瘍学会
ランチョンセミナー

- 腫瘍内科医のための -
乳癌ホルモン療法講座

腫瘍内科　渡辺 亨
twatanab@oncoloplan.com
浜松オンコロジーセンター長
http://www.oncoloplan.com

乳癌診療にどのように従事していますか

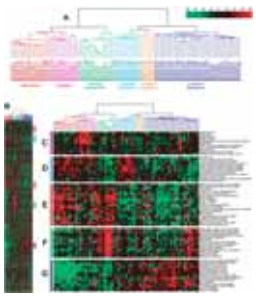
1. 術前薬物療法
2. 術後薬物療法
3. 再発後薬物療法
4. 肺転移症例の薬物療法
5. 緩和薬物療法
6. 従事していない
7. その他（業界関係者等）

次の疾患のうちホルモン療法が有効なのはどれか

1. 基底細胞様乳癌
2. 明細胞卵巣癌
3. 高齢者前立腺癌
4. 骨転移乳癌
5. 低分化子宮内膜癌
6. 管腔様乳癌
7. 閉経後乳癌

乳癌の病型分類

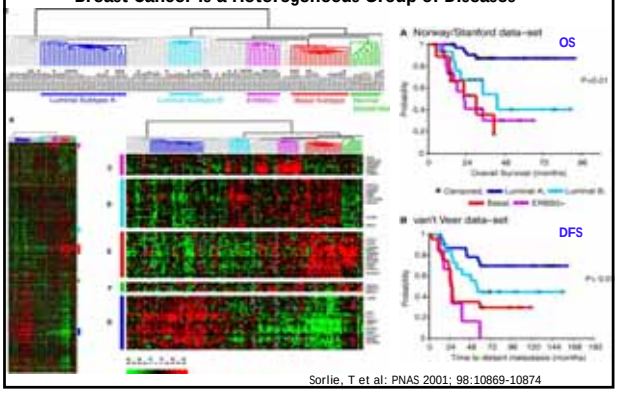
- Microarray を用いた遺伝子発現解析
- クラスター解析による病型分類
  - Luminal A
  - Luminal B
  - Basal-like
  - HER2 +



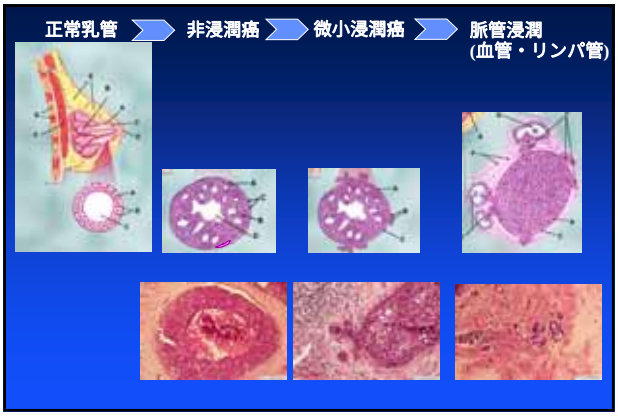
Sørlie, Therese et al. (2001) Proc. Natl. Acad. Sci. USA 98, 10869-10874

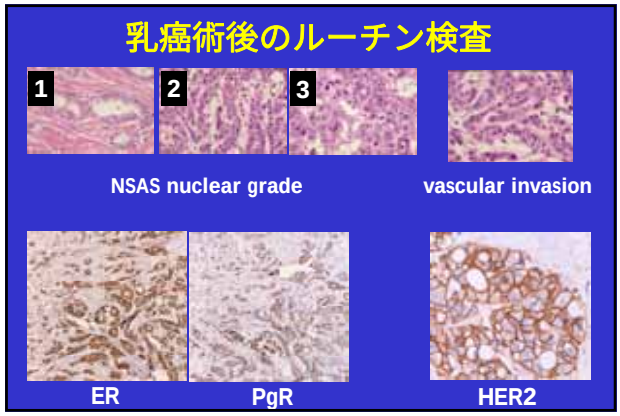
PNAS

Breast Cancer is a Heterogeneous Group of Diseases



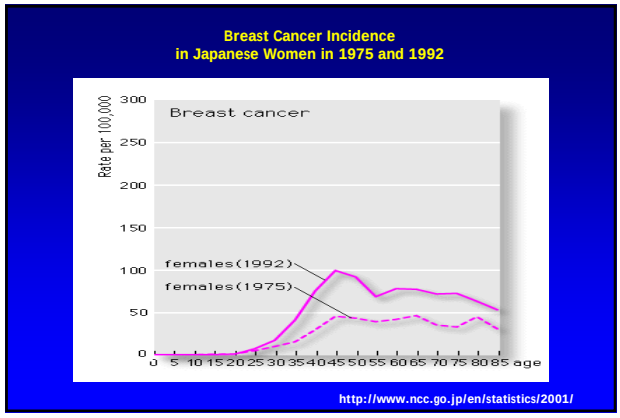
Sorlie, T et al: PNAS 2001; 98:10869-10874

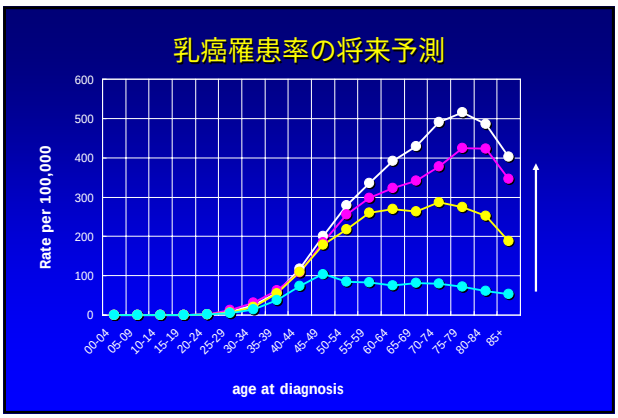


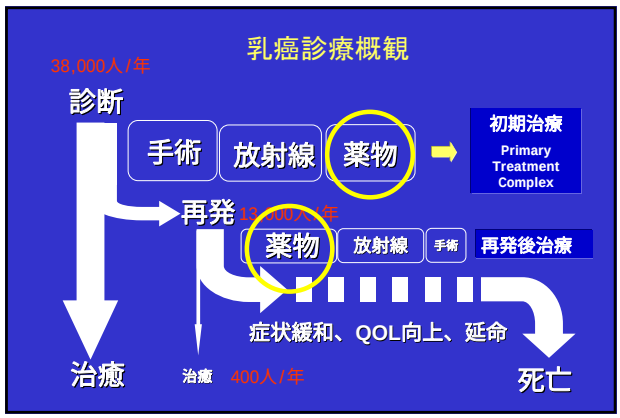


乳癌の病型分類とその一般化

		ホルモン受容体	
		陽性	陰性
HER2タンパク過剰発現	なし	Luminal A	Basal
	あり	Luminal B	HER2







William Halstead **(1852-1922)**

米国の外科医、 Johns Hopkins Universityにおける外科学教育に携わる。

無菌手術法、鼠径ヘルニア手術法、乳房切除術など、多くの手術方法を確立した。

乳癌の術式のうち、ハルステッド手術と呼ばれる方法は、乳房、大胸筋、小胸筋、腋窩軟部組織を一塊に切除する方法で、20世紀前半の標準的術式と考えられていた。

Halstead 理論

乳がんはまず局所皮膚からリンパ節に転移し次に遠隔臓器に転移する。

局所領域ﾘﾝﾊﾟ節はバリアとして機能し、

徹底した領域郭清が治癒率向上の鍵である。

Primary	原発巣
Local	局所
Regional	領域
Distant	遠隔

Bernard Fisher (1918-)

米国の外科医、 NSABP (National Surgical Adjuvant Bowel and Breast Project)を率い多くの臨床試験を実施

Halstead 手術 = 胸筋温存乳房切除術

胸筋温存乳房切除術 = 乳房温存術

手術単独 < 手術+術後化学療法

術後12週間のAC = 術後24週間のCMF

などをランダム化比較試験で検証した。

まだ切手には
なっていない

Fisher 理論

乳房に生じたがんは基底膜を破る(浸潤)や否やリンパ節、遠隔臓器に同時期に転移する

転移巣は微小転移として病状の早期より存在

早期からの全身治療が治癒率向上の鍵

Primary	原発巣
Metastatic	転移

St Gallen 2005

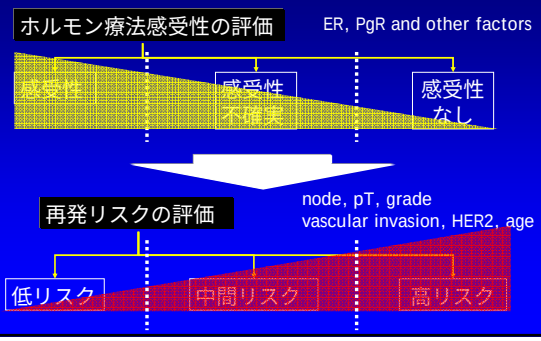
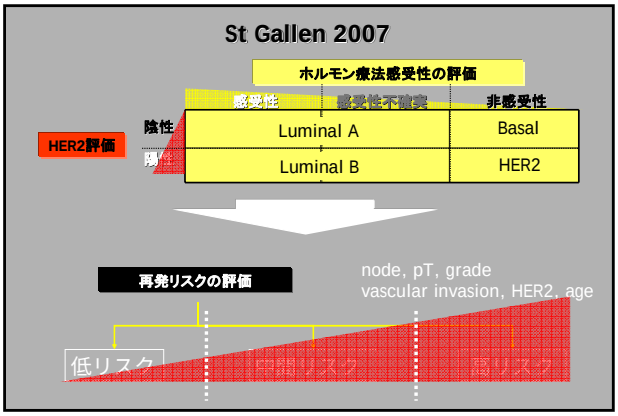
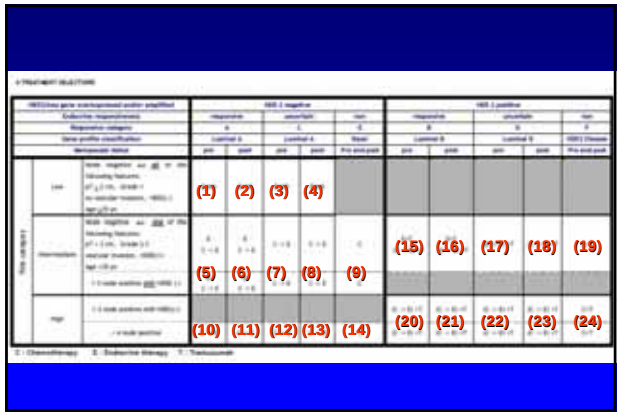


Table 3. Choice of treatment modalities 2005 (see text)

Risk category[a]	Endocrine responsive[b]	Endocrine response uncertain[b,c]	Endocrine non-responsive[b]
Low risk	ET Nil[d]	ET Nil[d]	Not applicable
Intermediate risk	ET alone, or CT → ET (CT + ET)[e]	CT → ET (CT + ET)[e]	CT
High risk	CT → ET (CT + ET)[e]	CT → ET (CT + ET)[e]	CT

St Gallen 2007





術後治療 24 通りの選択

$$3 \times 2 \times 3 \times 2 - 12$$

ENDOCRINE RESPONSIVENESS | HER2 | RISK CATEGORIES | MENOPAUSAL STATUS

治療選択問題
症例 1

57才　閉経後女性

浸潤性小葉癌

腫瘍径　3cm

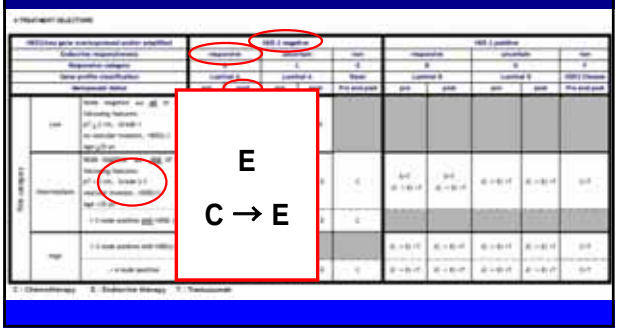
Grade 1

n = 1/12

ER (+++)　PgR　(+++)

HER2 (-)

症例 1 治療法の選択



アロマターゼ阻害剤

世代	非ステロイド系	ステロイド系
1	aminoglutethimide (日本非発売)	testolacotone (日本非発売)
2	fadrozole (ﾌｪﾏｰﾗ®)	formestane
3	anastrozole (ｱﾘﾐﾃﾞｯｸｽ®) **letrozole (ﾌｪﾏｰﾗ®)** vorozole (開発中止)	exemestane(ｱﾛﾏｼﾝ®)

閉経後乳癌
ホルモン療法

Evidence tells us to select:

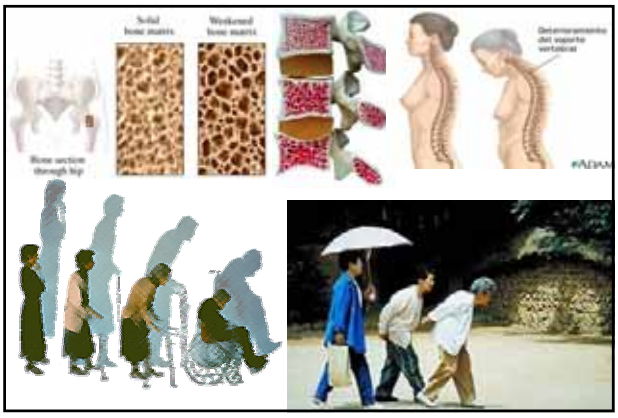
Letrozole	2.5 mg/日	5 年

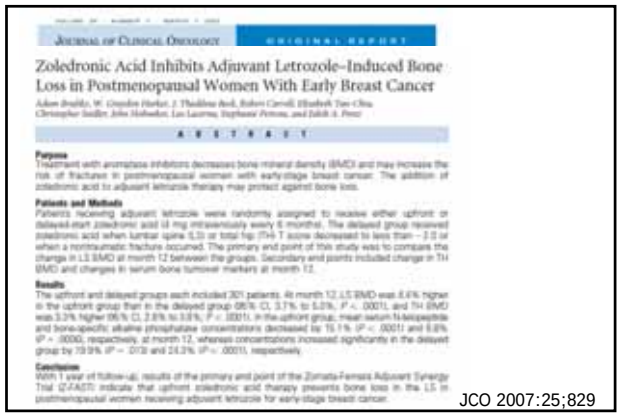
Consensus tells us to select:

Tamoxifen	20 mg/日	2-3年
Letrozole	2.5 mg/日	2-3年

Incidence of Worst Grade of Adverse Events among Patients Included in the Safety Analysis

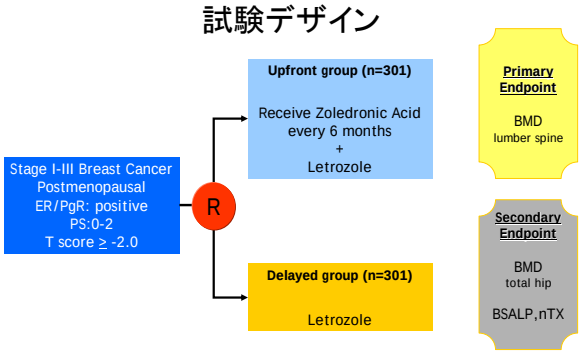
Grade	letrozole 1	2	3	4	5	any	%	tamoxifen 1	2	3	4	5	any	%	p
Bone fractures	—	141	70	—	—	211	8.6	—	105	36	—	—	141	5.8	<.001



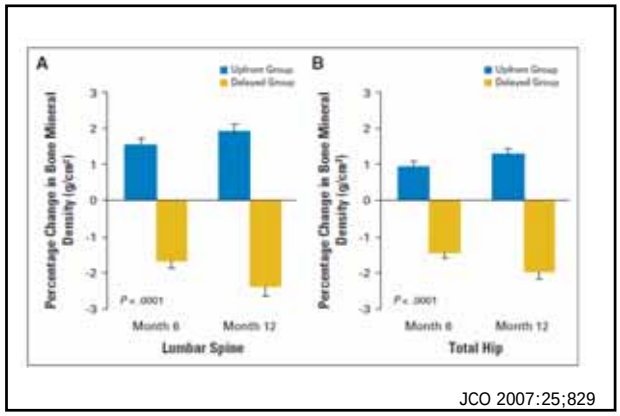


JCO 2007:25;829

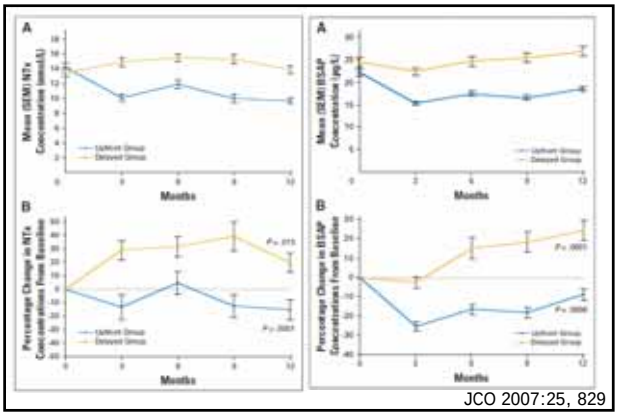
試験デザイン



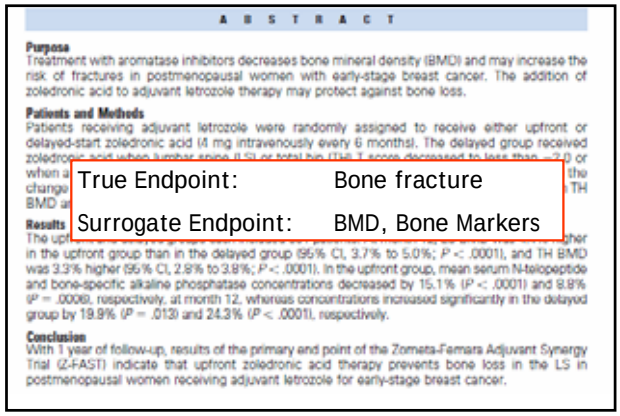
JCO 2007:25;829



JCO 2007:25;829



JCO 2007:25, 829



ABSTRACT

Purpose
Treatment with aromatase inhibitors decreases bone mineral density (BMD) and may increase the risk of fractures in postmenopausal women with early-stage breast cancer. The addition of zoledronic acid to adjuvant letrozole therapy may protect against bone loss.

Patients and Methods
Patients receiving adjuvant letrozole were randomly assigned to receive either upfront or delayed-start zoledronic acid (4 mg intravenously every 6 months). The delayed group received zoledronic acid when lumbar spine (LS) or total hip (TH) T score decreased to less than −2.0 or when a

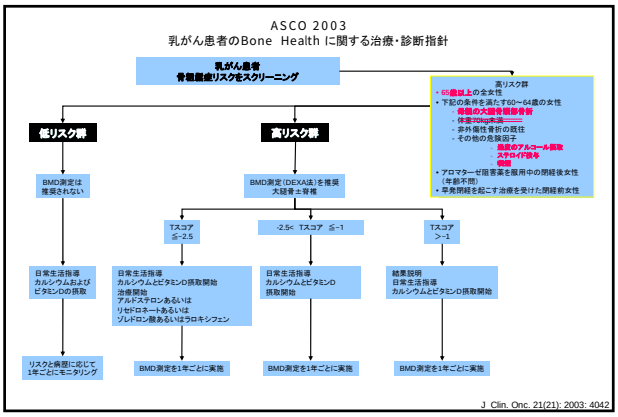
True Endpoint: Bone fracture

Surrogate Endpoint: BMD, Bone Markers

change TH BMD a

Results
The upf her in the upfront group than in the delayed group (95% CI, 3.7% to 5.0%; $P < .0001$), and TH BMD was 3.3% higher (95% CI, 2.8% to 3.8%; $P < .0001$). In the upfront group, mean serum N-telopeptide and bone-specific alkaline phosphatase concentrations decreased by 15.1% ($P < .0001$) and 9.8% ($P = .0006$), respectively, at month 12, whereas concentrations increased significantly in the delayed group by 19.9% ($P = .013$) and 24.3% ($P < .0001$), respectively.

Conclusion
With 1 year of follow-up, results of the primary end point of the Zometa-Femara Adjuvant Synergy Trial (Z-FAST) indicate that upfront zoledronic acid therapy prevents bone loss in the LS in postmenopausal women receiving adjuvant letrozole for early-stage breast cancer.



J Clin. Onc. 21(21): 2003: 4042

治療選択問題
症例 2

57才　閉経後女性

浸潤性乳管癌

腫瘍径　1.5 cm

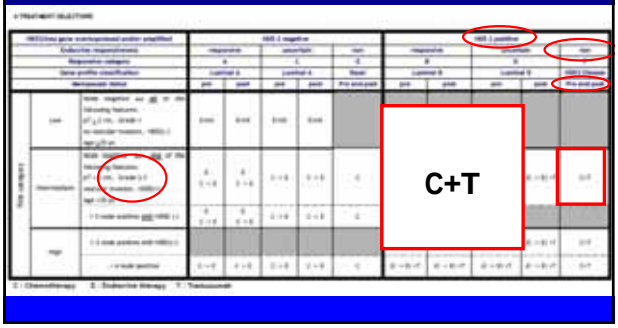
Grade 3

n = 0/12

ER (-)　PgR　(-)

HER2 (+++)

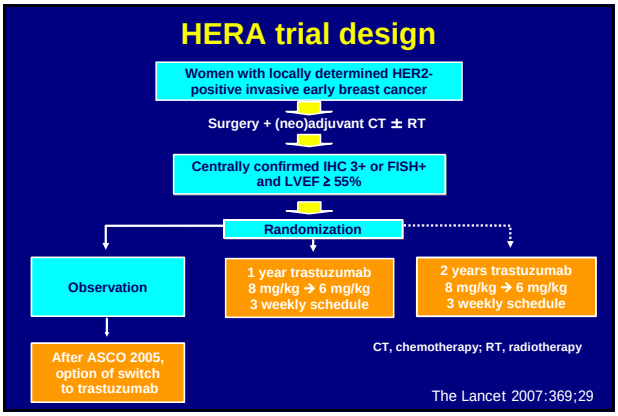
症例 2 治療法の選択

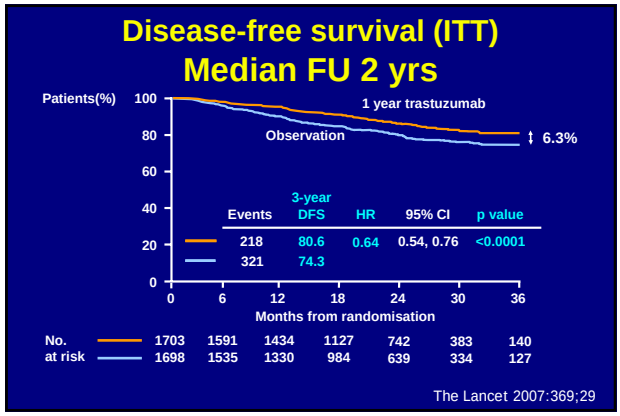


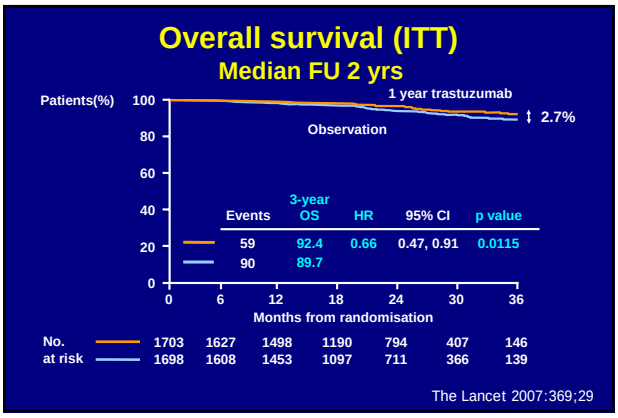
Trastuzumab Following Adjuvant Chemotherapy in HER2-Positive Early Breast Cancer (HERA Trial): Disease-Free and Overall Survival after 2 Year Median Follow-Up

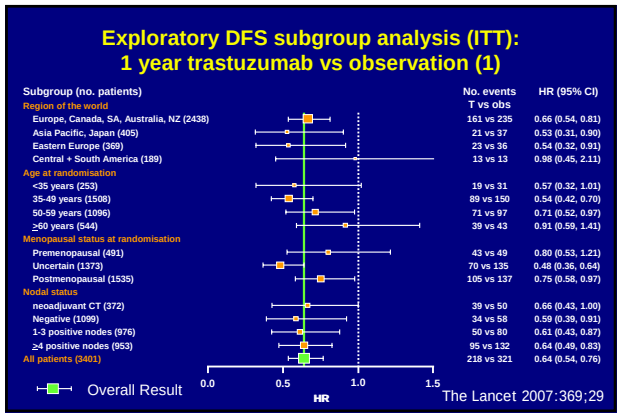
The HERA Study Team

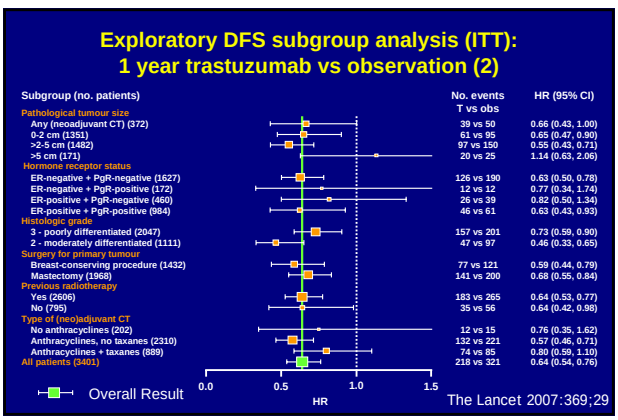
The Lancet 2007:369;29

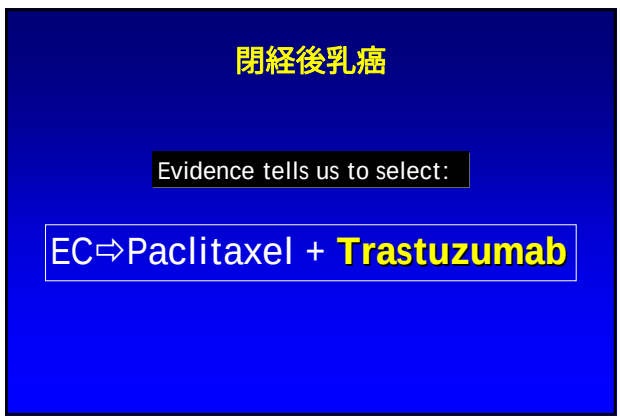

HERA trial design
Women with locally determined HER2-positive invasive early breast cancer
Surgery + (neo)adjuvant CT ± RT
Centrally confirmed IHC 3+ or FISH+ and LVEF ≥ 55%
Randomization
Observation
1 year trastuzumab 8 mg/kg → 6 mg/kg 3 weekly schedule
2 years trastuzumab 8 mg/kg → 6 mg/kg 3 weekly schedule
After ASCO 2005, option of switch to trastuzumab
CT, chemotherapy; RT, radiotherapy
The Lancet 2007:369;29


Disease-free survival (ITT)
Median FU 2 yrs
Patients(%)
1 year trastuzumab
Observation
6.3%
3-year
Events DFS HR 95% CI p value
218 80.6 0.64 0.54, 0.76 <0.0001
321 74.3
Months from randomisation
No. at risk
1703 1591 1434 1127 742 383 140
1698 1535 1330 984 639 334 127
The Lancet 2007:369;29


Overall survival (ITT)
Median FU 2 yrs
Patients(%)
1 year trastuzumab
Observation
2.7%
3-year
Events OS HR 95% CI p value
59 92.4 0.66 0.47, 0.91 0.0115
90 89.7
Months from randomisation
No. at risk
1703 1627 1498 1190 794 407 146
1698 1608 1453 1097 711 366 139
The Lancet 2007:369;29


Exploratory DFS subgroup analysis (ITT):
1 year trastuzumab vs observation (1)
Subgroup (no. patients)
No. events T vs obs
HR (95% CI)
Region of the world
Europe, Canada, SA, Australia, NZ (2438) 161 vs 235 0.66 (0.54, 0.81)
Asia Pacific, Japan (405) 21 vs 37 0.53 (0.31, 0.90)
Eastern Europe (369) 23 vs 36 0.54 (0.32, 0.91)
Central + South America (189) 13 vs 13 0.98 (0.45, 2.11)
Age at randomisation
<35 years (253) 19 vs 31 0.57 (0.32, 1.01)
35-49 years (1508) 89 vs 150 0.54 (0.42, 0.70)
50-59 years (1096) 71 vs 97 0.71 (0.52, 0.97)
≥60 years (544) 39 vs 43 0.91 (0.59, 1.41)
Menopausal status at randomisation
Premenopausal (491) 43 vs 49 0.80 (0.53, 1.21)
Uncertain (1373) 70 vs 135 0.48 (0.36, 0.64)
Postmenopausal (1535) 105 vs 137 0.75 (0.58, 0.97)
Nodal status
neoadjuvant CT (372) 39 vs 50 0.66 (0.43, 1.00)
Negative (1099) 34 vs 58 0.59 (0.39, 0.91)
1-3 positive nodes (976) 50 vs 80 0.61 (0.43, 0.87)
≥4 positive nodes (953) 95 vs 132 0.64 (0.49, 0.83)
All patients (3401) 218 vs 321 0.64 (0.54, 0.76)
0.0 0.5 1.0 1.5
HR
Overall Result
The Lancet 2007:369;29


Exploratory DFS subgroup analysis (ITT):
1 year trastuzumab vs observation (2)
Subgroup (no. patients)
No. events T vs obs
HR (95% CI)
Pathological tumour size
Any (neoadjuvant CT) (372) 39 vs 50 0.66 (0.43, 1.00)
0-2 cm (1351) 61 vs 95 0.65 (0.47, 0.90)
>2-5 cm (1482) 97 vs 150 0.55 (0.43, 0.71)
>5 cm (171) 20 vs 25 1.14 (0.63, 2.06)
Hormone receptor status
ER-negative + PgR-negative (1627) 126 vs 190 0.63 (0.50, 0.78)
ER-negative + PgR-positive (172) 12 vs 12 0.77 (0.34, 1.74)
ER-positive + PgR-negative (460) 26 vs 39 0.82 (0.50, 1.34)
ER-positive + PgR-positive (984) 46 vs 61 0.63 (0.43, 0.93)
Histologic grade
3 - poorly differentiated (2047) 157 vs 201 0.73 (0.59, 0.90)
2 - moderately differentiated (1111) 47 vs 97 0.46 (0.33, 0.65)
Surgery for primary tumour
Breast-conserving procedure (1432) 77 vs 121 0.59 (0.44, 0.79)
Mastectomy (1968) 141 vs 200 0.68 (0.55, 0.84)
Previous radiotherapy
Yes (2606) 183 vs 265 0.64 (0.53, 0.77)
No (795) 35 vs 56 0.64 (0.42, 0.98)
Type of (neo)adjuvant CT
No anthracyclines (202) 12 vs 15 0.76 (0.35, 1.62)
Anthracyclines, no taxanes (2310) 132 vs 221 0.57 (0.46, 0.71)
Anthracyclines + taxanes (889) 74 vs 85 0.80 (0.59, 1.10)
All patients (3401) 218 vs 321 0.64 (0.54, 0.76)
0.0 0.5 1.0 1.5
HR
Overall Result
The Lancet 2007:369;29


閉経後乳癌
Evidence tells us to select:
EC⇨Paclitaxel + Trastuzumab

Final Take-home message

1. 乳癌治療には細胞毒性抗癌剤、ホルモン剤、
分子標的薬剤が使用される。
2. 効果予測因子が確立されているので
「原因と結果の法則」が成り立つ。
3. 乳癌薬物療法で習得したノウハウは
他疾患の治療に応用できる。
4. **乳癌診療を勉強したい人は浜松オンコロジーセンターに来てほしい。（委細面談、待遇抜群、経験不問）**